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Review

Venous thromboembolism in brain tumor patients

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ABSTRACT

Venous thromboembolism (VTE) is a relatively common and well-described condition, affecting approximately 1–2% of the general population. VTE can lead to significant morbidity and death via pulmonary embolism (PE). During the post-operative period, VTE occurs at higher rates due to natural thrombotic responses to injury and limited post-operative mobility. In general, rates of post-operative VTE are higher in patients undergoing operations for cranial and spinal lesions than for lesions of other types, a phenomenon that is not fully explained. Proposed mechanisms include increased local synthesis of tissue factor in brain tumor patients and a higher rate of paresis in patients undergoing operations on the central nervous system. Several studies have demonstrated that other risk factors for VTE include age, sex, ethnicity, hospital stay length, and coagulation state. Tumor type and size have also been explored as potential risk factors. Despite higher rates of VTE development, neurosurgeons are often hesitant to prescribe post-operative anticoagulants for fear of hemorrhage. Here we review the literature on VTE in brain tumor patients, with a focus on their etiology, diagnosis, treatment, and prophylaxis. In most brain tumor patients, aggressive chemical and mechanical VTE prophylaxis is indicated in the post-operative period to prevent the formation of VTE.

1. Introduction

Venous thromboemboli (VTE) occur regularly in 1–2% of the general population, with an annual incidence of 1 in 500 [1,2]. VTE can cause death via pulmonary emboli (PE) or significant disability due to pain, edema, and post-thrombotic syndrome, a form of venous reflux that occurs secondary to deep vein thrombosis (DVT). VTE occurs at a higher rate during the post-operative period due to natural thrombotic responses to injury and limited post-operative mobility. Patients harboring brain tumors are more likely to develop VTE than patients who have cancers in other sites (Table 1) [3–24]. Studies have shown that other risk factors for VTE include age, sex, ethnicity, blood type, length of hospital stay, operative duration, and coagulation status [3,6,8–10,14,25–38]. Standard prophylactic measures for VTE include chemical anticoagulation, mechanical prophylaxis, and increased ambulation during the post-operative period [36,39–54].

This paper seeks to review the relevant and current literature on VTE in brain tumor patients, with particular focus on the risk factors and presenting symptoms of VTE, treatment options for those with VTE, and a review of current prophylactic measures for VTE.

2. Pathogenesis

Several factors are thought to drive the formation of VTE. Most prominently, these include venous stasis, blood hypercoagulability, and damage to blood vessel walls [2,55]. Unlike typical blood clots, which form as a collection of erythrocytes on a fibrin mesh, VTE develop in several laminar layers of platelets, leukocytes, and fibrin, which surround a nucleus of erythrocytes [2,56]. Venous blood velocity is much slower than arterial blood flow [57]. Combined with the surface of venous valves and the dilated sinuses of the lower extremities, this relative stasis has been proposed as a potential source of VTE [57]. Venous stasis and blood hypercoagulability promote adherence to collection sites, while damage to vessels exposes the collagen-rich interior of vascular walls. Collagen-rich walls have been reported to promote platelet aggregation, which further incites formation of VTE through collection of leukocytes [55,56].

Inflammation is another proposed contributor to the formation of VTE, in large part because of its role in promoting platelet reactivity and increasing circulating complexes, including tissue factor (TF) and fibrinogen. Bucek et al. demonstrated that the inflammatory marker C-reactive protein increases in patients with DVT and therefore can be considered a potential indicator of the presence of VTE [58]. The endothelium, which expresses pro- and anticoagulants, as well as vasoconstrictors and vasodilators, plays a

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Table 1
Rate of venous thromboembolism in patients with various types of cancer[^]

Cancer type/site	Diagnoses/100 hospitalizations		
	VTE	PE	DVT
Pancreas	4.3	1.2	3.5
Brain	**3.5**	**1.0**	**2.8**
Myeloproliferative, other lymphatic/hematopoetic	2.9	*	2.5
Stomach	2.7	0.7	2.3
Lymphoma, lymphosarcoma, reticulosarcoma	2.5	0.6	2.0
Uterus	2.2	0.5	1.8
Trachea, bronchus, lung	2.1	0.6	1.6
Esophagus	2.0	*	1.3
Prostate	2.0	0.6	1.6
Rectum, rectosigmoid junction, anus	2.1	0.7	1.4
Kidney	2.0	0.5	1.6
Colon	1.9	0.6	1.4
Ovary	2.0	0.5	1.6
Liver, gallbladder, intra- and extra-hepatic ducts	1.8	0.9	1.1
Leukemia	1.7	0.4	1.4
Breast (female)	1.7	0.4	1.3
Cervix	1.6	*	1.4
Bladder	1.0	0.3	0.8
Lip, oral cavity, pharynx	<0.6	*	*
No cancer	1.0	0.3	0.8

[^] Table adapted from Stein et al. Am J Med 2006;119:60–8 [15].
* Insufficient data.
DVT = deep vein thrombosis, PE = pulmonary embolism, VTE = venous thromboembolism.
Bold indicates VTE in brain cancer patients, the topic of this review.

prominent role in the development of VTE via inflammation. Wakefield et al. report that when the endothelium is disturbed, either functionally or mechanically, the endothelial surface vasoconstricts and reacts in a prothrombotic fashion. Endothelial cells release pro-thrombotic factors including platelet activating factor, endothelin-1 (a vasoconstrictor), von Willebrand factor, TF, and plasminogen activator inhibitor [55]. Injury to the endothelium also promotes surface expression of cell adhesion molecules like P-selectin and E-selectin, which promote leukocyte margination and adhesion [55]. The net effect of these inflammatory cascades following injury or disruption of venous vessels promotes VTE development.

3. VTE in brain tumor patients

Although VTE is relatively common in the general population, it is far more common during the post-operative period [25,27,39–42,51–53]. Proposed explanations for this phenomenon include limited post-operative mobility, which can promote venous stasis, and damage to endothelial tissue, as discussed above.

Several studies have shown that patients harboring brain tumors develop DVT at a higher rate than patients with cancer at other sites or patients undergoing procedures for diseases other than cancer (Table 1) [18,20,59]. Day et al. recently reported a VTE rate of 1.2% for lower extremity arthroplasties, and only 0.53% for shoulder arthroplasties [60]. In a study of patients undergoing operations for lung cancer, on the other hand, Christensen et al. reported a mean risk of 2.0% [61]. Stein et al. report the rate of VTE in patients with brain malignancies, on the other hand, to be 3.5 diagnoses per 100 hospitalizations [15]. In a separate study of more than 1,000 brain tumor patients, the rate of VTE was 19.4%, though this may be artificially elevated in part due to more aggressive surveillance for DVT and PE [17]. In an investigation of site-specific cancer and its relation to VTE formation, Petterson et al. found that malignancies of the brain resulted in one of the highest rates of VTE formation, even after adjusting for complicating factors like age and sex [23].

Many mechanisms have been proposed for the increased rate of VTE in patients with cancer. Several studies have investigated circulating microparticles (MP) in the blood, which originate from cancer cells and often express TF. In 2011, Sartori et al. studied the pro-coagulant activity of circulating MP in patients harboring glioblastoma multiforme (GBM). They found that MP activity levels increased in 63.6% of 61 patients who underwent resection of GBM, a statistically significant association ($chi^2 = 4.93$, $p = 0.026$) [62]. In 2004, Browd et al. demonstrated that DVT formation in patients undergoing neurosurgery is as high as 25%, with mortality rates from PE ranging from 9 to 50% [63]. A study by Khorana et al. of patients with pancreatic cancer further indicated that increased plasma TF – a physiologic initiator of coagulation – is correlated with development of VTE in the post-operative period [64]. The authors also suggest that cancer cells are a potential source of circulating TF, which could be an explanation for the increased rate of VTE in cancer patients. Not all cancers produce these pro-coagulant effects equally, however, which leads to the disparity in VTE rate between tumors of the brain and cancers of other sites. For example, studies have shown that high-grade tumors of the brain result in a higher concentration of TF, with an associated higher rate of VTE development [62]. A study of 1,000 patients undergoing operations for brain tumors showed a strong correlation between higher tumor grade and DVT development (Table 2) [14,17]. In this study, histologically benign tumors (for example meningiomas, pituitary adenoma) resulted in much lower rates of VTE development, suggesting that these patients are overall at a lower risk of VTE in the post-operative period.

4. Risk factors

Risk factors for VTE are well-described in the literature, and many studies have examined a range of variables for their effect on rate of VTE development (Table 3) [65]. The most commonly reported risk factor for VTE is age. In 1994, Kniffin et al. reported that the annual incidence rates per 1,000 from age 65 to 69 is 1.3 for PE and 1.8 for DVT. The incidence rates increased steadily with age: at age 85 to 89 years, the annual incidence rates were 2.8 and 3.1, respectively [29]. In 2004, a study by Stein et al. corroborated these results, demonstrating that patients aged 30 to 39 years have a two-fold higher risk of DVT or PE compared to younger patients, while patients 70 years or older have an 18- to 28-fold increase in risk of DVT or PE than those aged 20 to 29 years [66]. A separate

Table 2
Deep vein thrombosis incidence by brain tumor type[*]

Tumor type	DVT+/Total patients (%)
Metastasis	44/185 (23.8)
High grade glioma	53/248 (21.4)
Low grade glioma	5/28 (17.6)
Meningioma	16/196 (8.2)
High grade oligodendroglioma	3/15 (20.0)
Low grade oligodendroglioma	2/16 (12.5)
Mixed	3/9 (33.3)
Sarcoma	0/3 (0.0)
Schwanomma	4/22 (18.2)
Acoustic neuroma	0/1 (0.0)
Medulloblastoma	0/6 (0.0)
Lymphoma	8/27 (29.6)
Pituitary adenoma	0/10 (0.0)
Ependymoma	0/6 (0.0)
Hemangiopericytoma	1/4(25.0)
Choroid	0/3 (0.0)
Hemangioblastoma	2/9 (22.2)
Other	15/88 (17.0)

[*] Table adapted from Smith et al. J Clin Neurosci 2015;22:519–25 [17].
DVT = deep vein thrombosis.